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Wnt-4 and Ets-1 signaling pathways for regeneration after acute renal failure

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Ischemic acute renal failure (ARF) is the most common form of ARF in the adult population. The molecular mechanisms of tubular regeneration after ischemic renal injury remain largely unknown. An understanding of the mechanisms that lead to renal cell proliferation and regeneration will be necessary for the exploration of novel therapeutic strategies for the treatment of ARF. It has been suggested that regeneration processes may recapitulate developmental processes in order to restore organ or tissue function. The adult tubular epithelial cells have a potent ability of regenerate after cellular damage. We examined functional role of two developmental genes, Wnt-4 and Ets-1, in renal tubular regeneration in ARF. The Wnt-β-catenin pathway plays key roles in embryogenesis. Wnt-4 is known to be expressed in the mesonephric duct in the embryonic development. To clarify the significance of the Wnt-4-β-catenin pathway in ARF, we used a rat ARF model in vivo and LLC-PK1 cells as an in vitro model. After clamping left rat renal artery for 1 hour, we examined whole kidney homogenate and total RNA extracted at 3, 6, 12, 24, 48, and 72 hours after reperfusion by Western blot analysis and real-time reverse transcription-polymerase chain reaction (RT-PCR). Wnt-4 mRNA and protein expression were strongly increased at 3 to 12 hours and 6 to 24 hours after ischemia, respectively. In immunohistologic examination, Wnt-4 was expressed in the proximal tubules and coexpressed with aquaporin 1 and proliferating cell nuclear antigen (PCNA). Cyclin D1 and cyclin A were expressed at 12 to 48 hours after reperfusion. Furthermore, overexpression of Wnt-4 and β-catenin promoted the cell cycle and increased the promoter activity and protein expression of cyclin D1 and cyclin A in LLC-PK1 cells. These data suggest that the Wnt-4-β-catenin pathway plays a key role in the cell cycle progression of renal tubules in ARF. The Ets family of transcription factors is defined by a conserved DNA-binding Ets domain that forms a winged helix-turn-helix structure motif. The Ets family is involved in a diverse array of biologic functions, including cellular growth, migration, and differentiation. To clarify the significance of Ets-1 in ARF, we used a rat ARF model in vivo and LLC-PK1 cells as an in vitro model. Ets-1 mRNA and protein expression were strongly increased at 3 to 12 hours and 6 to 24 hours after the ischemia, respectively. In the immunohistologic examination, Ets-1 was expressed in the proximal tubules and coexpressed with PCNA. Furthermore, overexpression of Ets-1 promoted the cell cycle and increased the promoter activity and protein expression of cyclin D1 in LLC-PK1 cells. Ets-1 promoter activity increased between 3 hours and 6 hours in hypoxia, and hypoxia also induced changes in the Ets-1 protein level in LLC-PK1 cells. Taken together, these data suggest that Ets-1 plays a key role in the cell cycle progression of renal tubules in ARF. Our data suggest that Wnt-4-β-catenin and Ets-1 pathways regulate the transcription of cyclin D1 and control the regeneration of renal tubules in ARF. These developmental genes may play key roles in dedifferentiation and regeneration of the renal tubular cells after ARF.

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Search for genes expressed during progression and recovery in the diseased kidney

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Kidneys can recovery from some type of injury. After an acute glomerulonephritis or a short-term ischemia, damaged glomerulus or tubules recover their normal structures with proliferation of the survived cells and infiltration of extrarenal cells. On the other hand, a prolonged or continuous injury leads to a progressive renal disease. We have investigated molecular events in reversible and irreversible renal diseases and have made efforts to identify genes pivotal in promoting regeneration or progression of the renal diseases. To identify genes responsible for kidney regeneration, we surveyed the expression pattern of the "development" genes in ischemia-reperfusion model of rat kidney. The regeneration, molding, and maturation of the restored epithelium after renal ischemia injury have many parallels to the growth and maturation that takes place during kidney organogenesis. We found that leukemia inhibitory factor (LIF) and its receptor (LIFR) expression were up-regulated during the recovery phase after ischemia insult. The increased expression of LIF and LIFR was most marked in the outer medulla, especially in the S3 segment of the proximal tubules. In cultured rat renal epithelial NRK52E cells, LIF expression was enhanced during recovery after adenosine triphosphate (ATP) depletion. Blockade of endogenous LIF with a neutralizing antibody significantly reduced the cell number and DNA synthesis during the recovery period. These results suggest that LIF participates in the regeneration process after tubular injury [Yoshino J, Monkawa T, Tsuji M, *et al*: Leukemia inhibitory factor is involved in tubular regeneration after experimental acute renal failure. *J Am Soc Nephrol* 14:3090–3101, 2003]. To search for genes playing important roles in progression of renal diseases, we compared gene expression profiles between an irreversible model and a reversible model of anti-Thy-1 glomerulonephritis using a microarray technology. A single intravenous injection of anti-Thy-1 monoclonal antibody 1-22-3 is known to cause a reversible mesangial proliferative glomerulonephritis. However, monoclonal antibody 1-22-3 injection followed by unilateral nephrectomy leads to progressive glomerulosclerosis with an irreversible course. Among 4854 rat genes on the microarray slide, 189 genes were differentially expressed. The differentially expressed genes were classified into five clusters based on their expression patterns. One of the clusters included genes the expression of which was markedly up-regulated in